REMARKS

Claims 1-52 are pending in the application. Claims 10-41 and 46-52 have been withdrawn by the Examiner as directed to a non-elected invention. Reconsideration of the claims in view of the following Remarks is requested.

Enablement

Claims 1-9 and 42-45 were rejected under 35 USC § 112, first paragraph, for alleged lack of enablement. The Examiner contends that the present invention would require undue experimentation to practice as claimed, because one of skill in the art would recognize that administration of a Dkk-1 antagonist would exacerbate or induce cancer. Applicants traverse this rejection.

The Examiner "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *MPEP 2164.04*. A finding that further experimentation is necessary to practice an invention is insufficient to question the enablement of the claims. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *MPEP 2164.01*. Moreover, to establish enablement, the Applicants "need not demonstrate that the invention is completely safe." *MPEP 2164.01(c)*. The safety considerations taken into account by a regulatory body such as the FDA are "different from those made by the PTO in determining whether a claim is enabled." *MPEP 2164.05* (citing *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994)("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].")). In a utility context, the MPEP also states that an Applicant need not "demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans." *MPEP 2107.01 III*.

The present claims are directed to methods of treating insulin resistance or hypoinsulinemia, or methods of repairing or regenerating muscle, comprising administering a Dkk-1 antagonist. In light of the foregoing guidelines, the present claims are clearly enabled by the specification. Applicants respectfully submit there is no basis in the requirements for enablement as laid out in the MPEP, and in the caselaw, for questioning the enablement of a method of treating a medical disorder, based merely upon an assertion that such treatment may

lead to undesirable side effects. The MPEP clearly teaches that Applicants need not demonstrate that the claimed use would not cause or exacerbate cancer or any other adverse effect.

Rather, the present claims satisfy the requirements of 35 U.S.C. 112, first paragraph if the disclosure enables the use as claimed, i.e. the treatment of insulin resistance or hypoinsulinemia, or methods of repairing or regenerating muscle. By this standard, the present claims are enabled. Insulin resistance is a state characterized by normal or elevated blood glucose levels that persist in the presence of normal or elevated levels of insulin, such that basal or insulin-stimulated glycogen synthesis, or both, are lowered to subnormal levels (page 2, lines 26-30 of the specification).

The present specification provides data demonstrating that muscle cells treated with Dkk-1 exhibited insulin resistance (Example 1; page 50, lines 18-19). The specification also discloses that administration of Dkk-1 lowered levels of basal and insulin-stimulated glucose uptake in L6 muscle cells by inhibiting Akt, a known key intermediate in the insulin-signaling pathway (page 50, line 30 through page 51, line 2). Therefore, the Applicants have provided evidence directly linking the activity of Dkk-1 to the reduced glucose uptake characteristic of insulin resistance. Moreover, the specification also provides *in vivo* data demonstrating that intravenous injection of recombinant Dkk-1 in mice resulted in impaired glucose tolerance and reduced insulin production (page 48, lines 13-24 and Figs. 11A and 11B). Therefore, one of skill in the art would reasonably predict from reading Applicants' disclosure that administration of Dkk-1 antagonists as claimed would increase levels of basal and insulin-stimulated glucose uptake, a result that is synonymous with a decrease in insulin resistance.

Furthermore, the Applicants have also disclosed that intravenous injection of Dkk-1 in mice altered expression of multiple muscle-specific genes that were consistent with results seen in L6 muscle cells, providing evidence that Dkk-1 affects muscle differentiation both *in vitro* and *in vivo* (page 48, lines 25-36).

For the foregoing reasons, Applicants submit that the present claims are fully enabled by the specification.

Moreover, the Applicants respectfully disagree with the Examiner's assertion that one of skill in the art would conclude that downregulation of Dkk-1 would be unwise. Indeed, one of skill in the art would recognize that downregulation of Dkk-1 may in fact be useful in cancer therapies. Applicants submit with this response Tian et al (*NEJM* 2003; 349:2483-2494).

Relying on citations to references dating from 1986 to 1992, Tian et al. states that lung, breast, prostate cancer, and multiple myeloma were known to cause osteoblastic or osteolytic lesions in bone, and that these lesions are associated with decreased number and function of osteoblasts (first full paragraph). Citing to Cadigan et al. (*Genes Dev* 1997;11:3286-3305)., Tian et al. further notes that the Wnt signaling pathway was known to be important for the growth and differentiation of osteoblasts. *Id.* Therefore, one of skill in the art at the time of the present invention would have concluded, based on the knowledge in the art, that stimulation of the Wnt signaling pathway could be useful in treating cancer characterized by osteolytic lesions.

Indeed, in light of these teachings of the prior art, Tian et al. proceeded to study patterns of gene expression in myeloma cells, and disclosed that "[t]he production of DKK1, an inhibitor of osteoblast differentiation, by myeloma cells is associated with the presence of lytic bone lesions in patients with multiple myeloma."

Applicants also submit with this response a media article from *Reuters Health* discussing the findings of Tian et al. This article quotes a physician from the University of Arkansas for Medical Science as stating that "[w]e now have definitive evidence of a molecular mechanism for myeloma-associated bone destruction. Knowing the molecule that causes the pathology means we can develop drugs that specifically antagonize DKK1 function."

Consequently, Applicants submit that one of skill in the art would readily recognize that antagonists of Dkk-1 may in fact be useful in cancer treatment therapies.

Applicants respectfully submit, therefore, that the Examiner has not met the necessary burden to question the enablement of the claims, for at least the foregoing reasons. Withdrawal of the rejection is therefore requested.

SUMMARY

Applicants submit that all claims are in condition for allowance, and notice to that effect is earnestly solicited. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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